Figure 1

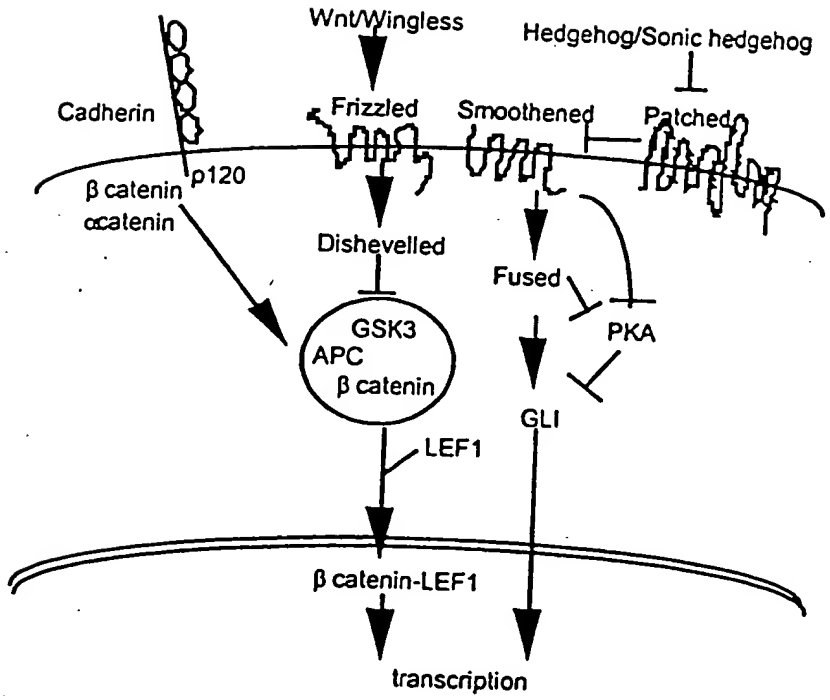

Wnt/Wingless
Hedgehog/Sonic hedgehog
Cadherin
Frizzled
Smoothened
Patched
β catenin
p120
∝catenin
Dishevelled
Fused
GSK3
APC
β catenin
PKA
GLI
LEF1
β catenin-LEF1
transcription

Figure 2a

Alignment of several frizzled family members

```
                  |->        amino terminal domain
fz3/mouse     --------------------MAVSWIVFDLWLLTVFLG---QIGGHS--------LFSCE
fz4/mouse     ------MAWPGTGPS---SRGAPGGVGLRLGLLLQFLLLLRPTLGFGD-----EEERRCD
fz8/mouse     ---------MEWGYL-----LEVTSLLAALAVLQRSSG-AAAASAK---------ELACQ
fz5/human     ---------MARPDP-----SAPPSLL--LLLLAQLVG-RAAAASK---------APVCQ
fzd9/human    -----MAVAPLRGALLLWQLLAAGGAALEIGRFD-------PERGRG--------AAPCQ
fz1/rat       LEAPLLLGVRAQPAG---QVSG-PGQQRPPPPQPQQGG--QQYNGERG--ISIPDHGYCQ
fz2/rat       --------MRARSAL---PRSALPRLLLPLLLLPAAGP--AQFHGEKG--ISIPDHGFCQ
fz/Dros       ILPTLIQGVQRYDQS---PLDASPYYRSGGGLMASSG---TELDG-------LPHHNRCE
fz2/Dros/     GLVLLLTSCRADGPL-----HSADHGMGGMGMGGHGLD-ASPAPGYGVPAIPKDPNLRCE
                                                                        *:

              _________________________________CRD__________________________
fz3/mouse     PITLRMCQDLPYNTTFMPNLLNHYDQQTAALAMEPFHPMVNLDCSRDFRPFLCALYAPIC
fz4/mouse     PIRIAMCQNLGYNVTKMPNLVGHELQTDAELQLTTFTPLIQYGCSSQLQFFLCSVYVPMC
fz8/mouse     EITVPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPDLKFFLCSMYTPIC
fz5/human     EITVPMCRGIGYNLTHMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPDLRFFLCTMYTPIC
fzd9/human    AVEIPMCRGIGYNLTRMPNLLGHTSQGEAAAELAEFAPLVQYGCHSHLRFFLCSLYAPMC
fz1/rat       PISIPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVC
fz2/rat       PISIPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVC
fz/Dros       PITISICKNIPYNMTIMPNLIGHTKQEEAGLEVHQFAPLVKIGCSDDLQLFLCSLYVPVC
fz2/Dros/     EITIPMCRGIGYNMTSFPNEMNHETQDEAGLEVHQFWPLVEIKCSPDLKFFLCSMYTPIC
               : :   * .: **    :**   .*   *   *    :   : *:::  *     : :**:    *:*

              ____________________CRD___________________________
fz3/mouse     M-EYGRVTLPCRRLCQRAYSECSKLMEMFG-VPWPEDMECSRFPDCD-EPYPRLVDLN--
fz4/mouse     TEKINIPIGPCGGMCLSVKRRCEPVLREFG-FAWPDTLNCSKFPPQN-DHNHMCMEGP--
fz8/mouse     LEDYKKPLPPCRSVCERAKAGCAPLMRQYG-FAWPDRMRCDRLPEQG-NPDTLCMDYN-R
fz5/human     LPDYHKPLPPCRSVCERAKAGCSPLMRQYG-FAWPERMSCDRLPVLGRDAEVLCMDYN-R
fzd9/human    TDQVSTPIPACRPMCEQARLRCAPIMEQFN-FGWPDSLDCARLPTRN-DPHALCMEAPEN
fz1/rat       T-VLEQALPPCRSLCERA-QGCEALMNKFG-FQWPDTLKCEKFPVHG--AGELCVGQNTS
fz2/rat       T-VLEQAIPPCRSICERARQGCEALMNKFG-FQWPERLRCEHFPRHG--AEQICVGQNHS
fz/Dros       T-ILERPIPPCRSLCESA-RVCEKLMKTYN-FNWPENLECSKFPVHG--GEDLCVAENTT
fz2/Dros/     LEDYHKPLPVCRSVCERARSGCAPIMQQYS-FEWPERMACEHLPLHG-DPDNLCMEQPSY
                           *   :*    .    *                **. :  *   :*               :

fz3/mouse     ------------------------------------------------LVGDPTE---
fz4/mouse     ---GDEE-----------------------------------------VPLPHKTP-
fz8/mouse     TDLTTAAPSPPRRLPPPPPPGEQPPSGSGHSRPPGARPPHRGGSSRGSGDAAAAPPSRGG
fz5/human     SEATTAPPRP---FPAKP---TLP--G-----PP-------------G----APAS-GG
fzd9/human    ATAGPAEPHK----GLGM----LP-------------------------VAPRPARPPG
fz1/rat       DKGTPTPSL-------------L-------------------------PEFWTSNPQHG
fz2/rat       EDG--TPAL-------------L-------------------------TTAPPSGLQPG
fz/Dros       SSA---------------------------------------------STAATPTRSVA
fz2/Dros/     TEAGSGGSSG----GSGG---SGSGSGSGGKRKQGGSGSGGSGAGGSSGSTSTKPCR-GR
```

Figure 2b

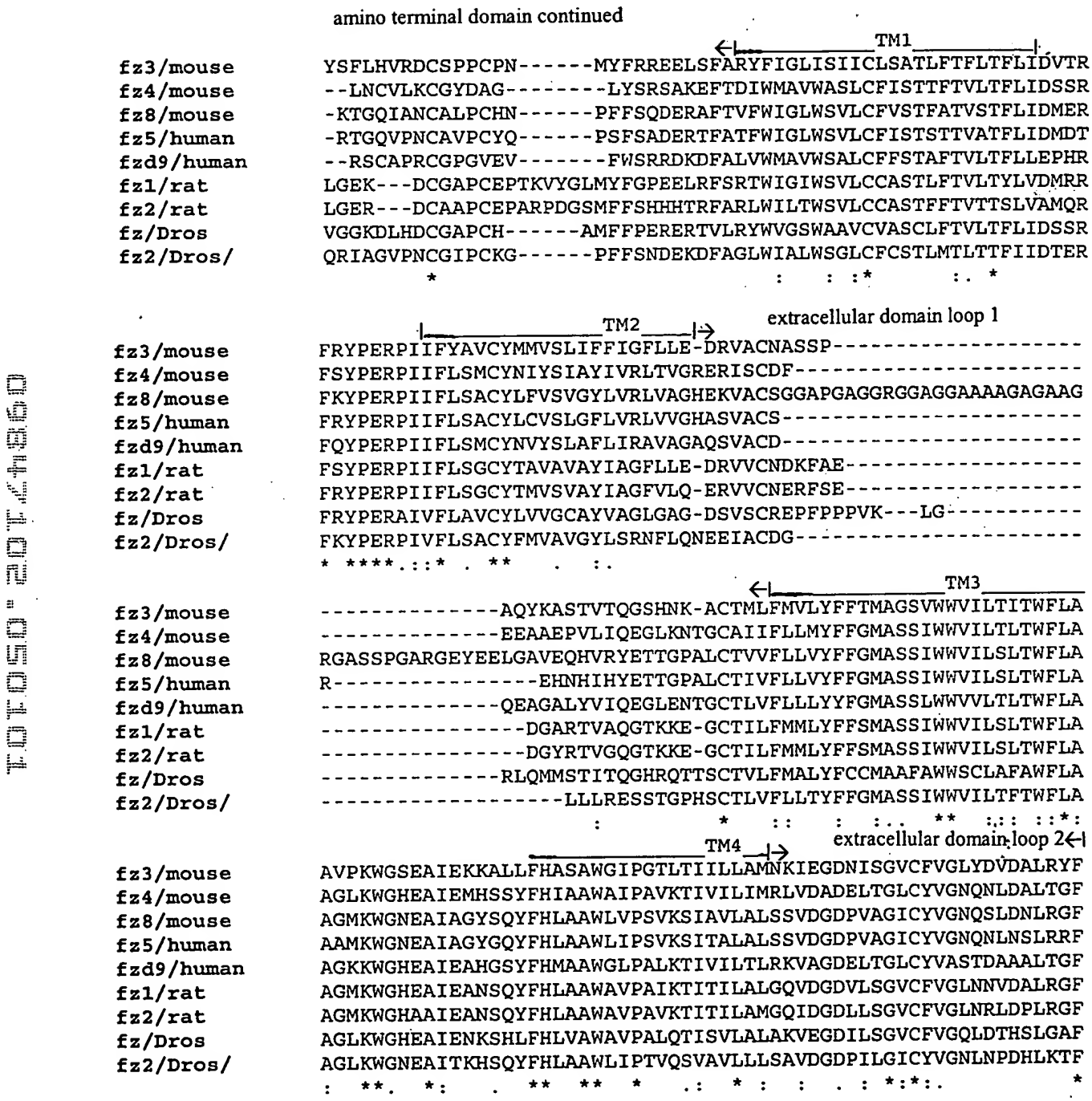

amino terminal domain continued
TM1
fz3/mouse YSFLHVRDCSPPCPN------MYFRREELSFARYFIGLISIICLSATLFTFLTFLIDVTR
fz4/mouse --LNCVLKCGYDAG--------LYSRSAKEFTDIWMAVWASLCFISTTFTVLTFLIDSSR
fz8/mouse -KTGQIANCALPCHN------PFFSQDERAFTVFWIGLWSVLCFVSTFATVSTFLIDMER
fz5/human -RTGQVPNCAVPCYQ------PSFSADERTFATFWIGLWSVLCFISTSTTVATFLIDMDT
fzd9/human --RSCAPRCGPGVEV-------FWSRRDKDFALVWMAVWSALCFFSTAFTVLTFLLEPHR
fz1/rat LGEK---DCGAPCEPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMRR
fz2/rat LGER---DCAAPCEPARPDGSMFFSHHHTRFARLWILTWSVLCCASTFFTVTTSLVAMQR
fz/Dros VGGKDLHDCGAPCH------AMFFPERERTVLRYWVGSWAAVCVASCLFTVLTFLIDSSR
fz2/Dros/ QRIAGVPNCGIPCKG------PFFSNDEKDFAGLWIALWSGLCFCSTLMTLTTFIIDTER
TM2
extracellular domain loop 1
fz3/mouse FRYPERPIIFYAVCYMMVSLIFFIGFLLE-DRVACNASSP----------
fz4/mouse FSYPERPIIFLSMCYNIYSIAYIVRLTVGRERISCDF----------
fz8/mouse FKYPERPIIFLSACYLFVSVGYLVRLVAGHEKVACSGGAPGAGGRGGAGGAAAAGAGAAG
fz5/human FRYPERPIIFLSACYLCVSLGFLVRLVVGHASVACS----------
fzd9/human FQYPERPIIFLSMCYNVYSLAFLIRAVAGAQSVACD----------
fz1/rat FSYPERPIIFLSGCYTAVAVAYIAGFLLE-DRVVCNDKFAE----------
fz2/rat FRYPERPIIFLSGCYTMVSVAYIAGFVLQ-ERVVCNERFSE----------
fz/Dros FRYPERAIVFLAVCYLVVGCAYVAGLGAG-DSVSCREPFPPPVK---LG----------
fz2/Dros/ FKYPERPIVFLSACYFMVAVGYLSRNFLQNEEIACDG----------
TM3
fz3/mouse ----------AQYKASTVTQGSHNK-ACTMLFMVLYFFTMAGSVWWVILTITWFLA
fz4/mouse ----------EEAAEPVLIQEGLKNTGCAIIFLLMYFFGMASSIWWVILTLTWFLA
fz8/mouse RGASSPGARGEYEELGAVEQHVRYETTGPALCTVVFLLVYFFGMASSIWWVILSLTWFLA
fz5/human R----------EHNHIHYETTGPALCTIVFLLVYFFGMASSIWWVILSLTWFLA
fzd9/human ----------QEAGALYVIQEGLENTGCTLVFLLLYYFGMASSLWWVVLTLTWFLA
fz1/rat ----------DGARTVAQGTKKE-GCTILFMMLYFFSMASSIWWVILSLTWFLA
fz2/rat ----------DGYRTVGQGTKKE-GCTILFMMLYFFSMASSIWWVILSLTWFLA
fz/Dros ----------RLQMMSTITQGHRQTTSCTVLFMALYFCCMAAFAWWSCLAFAWFLA
fz2/Dros/ ----------LLLRESSTGPHSCTLVFLLTYFFGMASSIWWVILTFTWFLA
TM4
extracellular domain loop 2
fz3/mouse AVPKWGSEAIEKKALLFHASAWGIPGTLTIILLAMNKIEGDNISGVCFVGLYDVDALRYF
fz4/mouse AGLKWGHEAIEMHSSYFHIAAWAIPAVKTIVILIMRLVDADELTGLCYVGNQNLDALTGF
fz8/mouse AGMKWGNEAIAGYSQYFHLAAWLVPSVKSIAVLALSSVDGDPVAGICYVGNQSLDNLRGF
fz5/human AAMKWGNEAIAGYGQYFHLAAWLIPSVKSITALALSSVDGDPVAGICYVGNQNLNSLRRF
fzd9/human AGKKWGHEAIEAHGSYFHMAAWGLPALKTIVILTLRKVAGDELTGLCYVASTDAAALTGF
fz1/rat AGMKWGHEAIEANSQYFHLAAWAVPAIKTITILALGQVDGDVLSGVCFVGLNNVDALRGF
fz2/rat AGMKWGHAAIEANSQYFHLAAWAVPAVKTITILAMGQIDGDLLSGVCFVGLNRLDPLRGF
fz/Dros AGLKWGHEAIENKSHLFHLVAWAVPALQTISVLALAKVEGDILSGVCFVGQLDTHSLGAF
fz2/Dros/ AGLKWGNEAITKHSQYFHLAAWLIPTVQSVAVLLLSAVDGDPILGICYVGNLNPDHLKTF

Figure 2c

```
                  ________________TM5____                                      _______
fz3/mouse     VLAPLCLYVVVGVSLLLAGIISLNRVRIEIPLEKE-----NQDKLVKFMIRIGVFSILYL
fz4/mouse     VVAPLFTYLVIGTLFIAAGLVALFKIRSNLQK-DG----TKTDKLERLMVKIGVFSVLYT
fz8/mouse     VLAPLVIYLFIGTMFLLAGFVSLFRIRSVIKQQGGP---TKTHKLEKLMIRLGLFTVLYT
fz5/human     VLGPLVLYLLVGTLFLLAGFVSLFRIRSVIKQ-GG----TKTDKLEKLMIRIGIFTLLYT
fzd9/human    VLVPLSGYLVLGSSFLLTGFVALFHIRKIMKT-GG----TNTEKLEKLMVKIGVFSILYT
fz1/rat       VLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKH-DG----TKTEKLEKLMVRIGVFSVLYT
fz2/rat       VLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKH-DG----TKTEPLERLMVRIGVFSVLYT
fz/Dros       LILPLCIYLSIGALFLLAGFISLFRIRTVMKT-DG----KRTDKLERLMLRIGFFSGLFI
fz2/Dros/     VLAPLFVYLVIGTTFLMAGFVSLFRIRSVIKQQGGVGAGVKADKLEKLMIRIGIFSVLYT
              :  *    : :*  :   .  :*  ::  :              . : ::  :: .*: *:
              _____TM6_______|->     extracellular domain loop 3          <-|_____
fz3/mouse     VPLLVVIGCYFYEQAYRGIWETTWIQERCREYHIPCPYQVTQMS-------RPDLILFLM
fz4/mouse     VPATCVIACYFYEISNWALFRYSADDS-------------------------NMAVEML
fz8/mouse     VPAAVVVACLFYEQHNRPRWEATHNCPCLRDLQPDQARR-------------PDYAVFML
fz5/human     VPASIVVACYLYEQHYRESWEAALTCACPGHDTGQPRAK-------------PEYWVLML
fzd9/human    VPATCVIVCYVYERLNMDFWRLRATEQPCAAAAGPGGRRDCSLP----GGSVPTVAVFML
fz1/rat       VPATIVIACYFYEQAFRDQWERSWVAQSCKSYAIPCPHLQGGGGVPPHPPMSPDFTVFMI
fz2/rat       VPATIVIACYFYEQAFREHWERSWVSQHCKSLAIPCPAHYT-------PRTSPDFTVYMI
fz/Dros       LPAVGLLGCLFYEYYNFDEWMIQWHRDICKPFSIPCPAARAPGS----PEARPIFQIFMV
fz2/Dros/     VPATIVIGCYLYEAAYFEDWIKALACPCAQVK--GPGKK-------------PLYSVLML
               *     : . . *                                           ::
              __________TM7____
fz3/mouse     KYLMALIVGIPSIFWVGSKKTCFEWASFFHGRRKKEIVNESRQVLQEPDFAQSLLRDPNT
fz4/mouse     KIFMSLLVGITSGMWIWSAKTLHTWQKCS-----------NRLVNSGKVK-----REKRG
fz8/mouse     KYFMCLVVGITSGVWVWSGKTLESWRALC-----------TRCCWASKGAAVGAGAGGSG
fz5/human     KYFMCLVVGITSGVWIWSGKTVESWRRFT-----------SRCCCRPR-------RGHK-
fzd9/human    KIFMSLVVGITSGVWVWSSKTFQTWQSLC-----------YRKIAAGRARA----KACRA
fz1/rat       KYLMTLIVGITSGFWIWSGKTLNSWRKFY-----------TRLTNSK--------QGETT
fz2/rat       KYLMTLIVGITSGFWIWSGKTLHSWRKFY-----------TRLTNSR--------HGETT
fz/Dros       KYLCSMLVGVTSSVWLYSSKTMVSWRNFV-----------ERLQGKEPRT-----RAQAY
fz2/Dros/     KYFMALAVGITSGVWIWSGKTLESWRRFW-----------RRLLGAPDRTGANQALIKQR
              : :  :  *  : .*: * **   :
```

Figure 3

Sequence alignment of a portion of the aminoterminal extracellular region of human Frizzled receptors

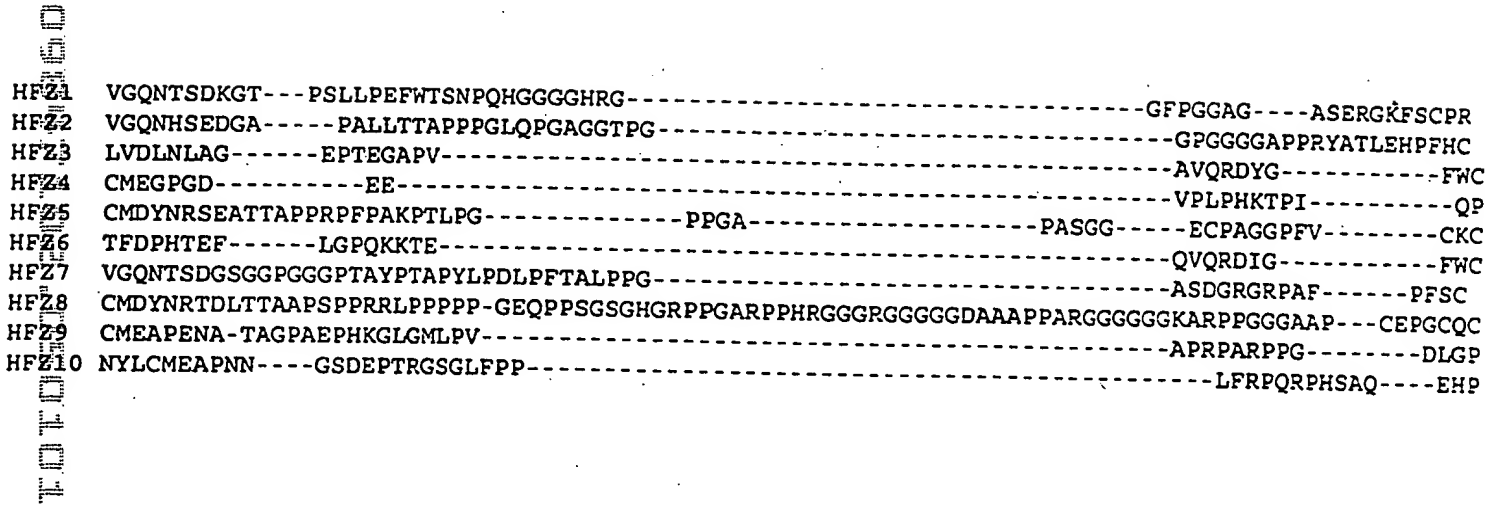


Figure 4

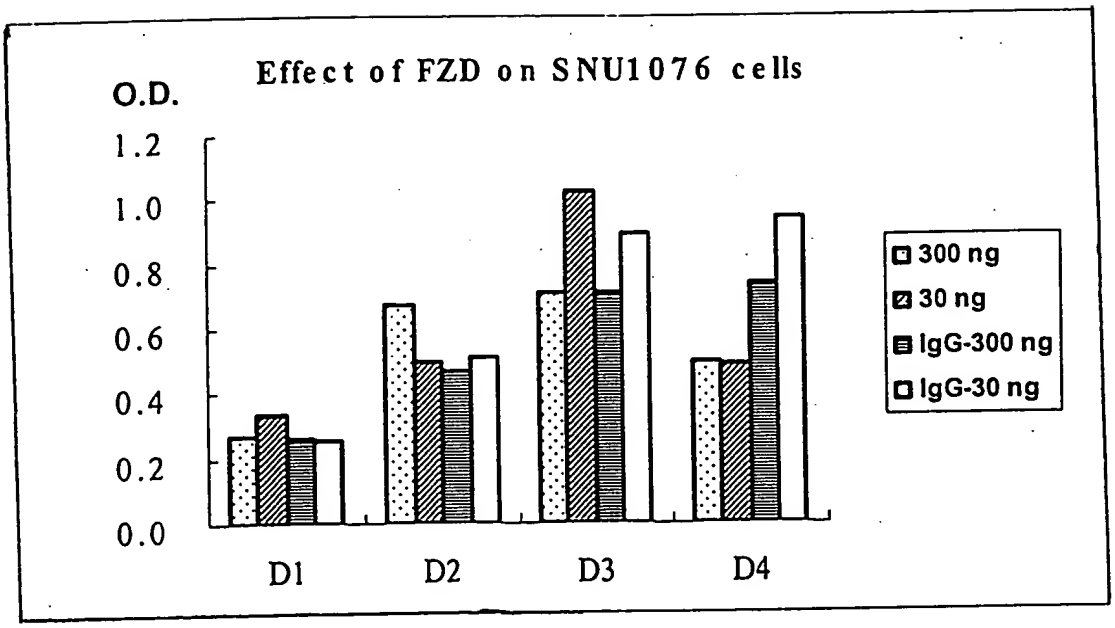

Effect of FZD on SNU1076 cells
O.D.
1.2
1.0
0.8
0.6
0.4
0.2
0.0
D1
D2
D3
D4
300 ng
30 ng
IgG-300 ng
IgG-30 ng

Figure 5

Effect of antibodies SNU 1076 Cells

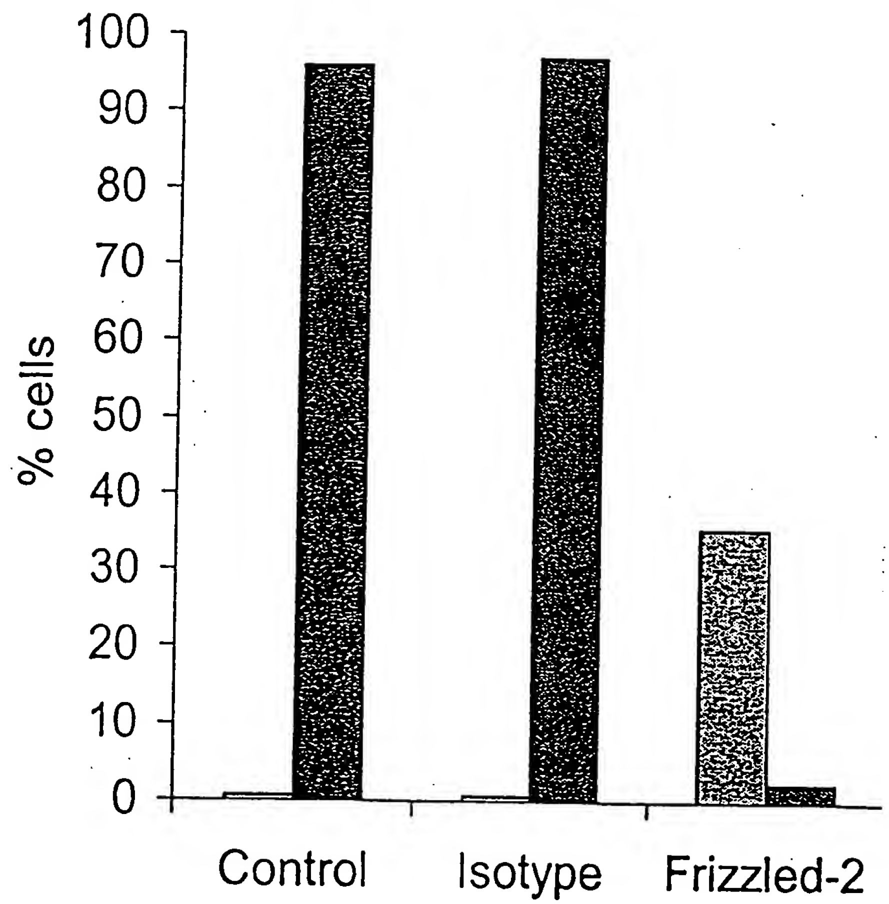


Figure 6

Effect of antibodies on SNU 1076 cells

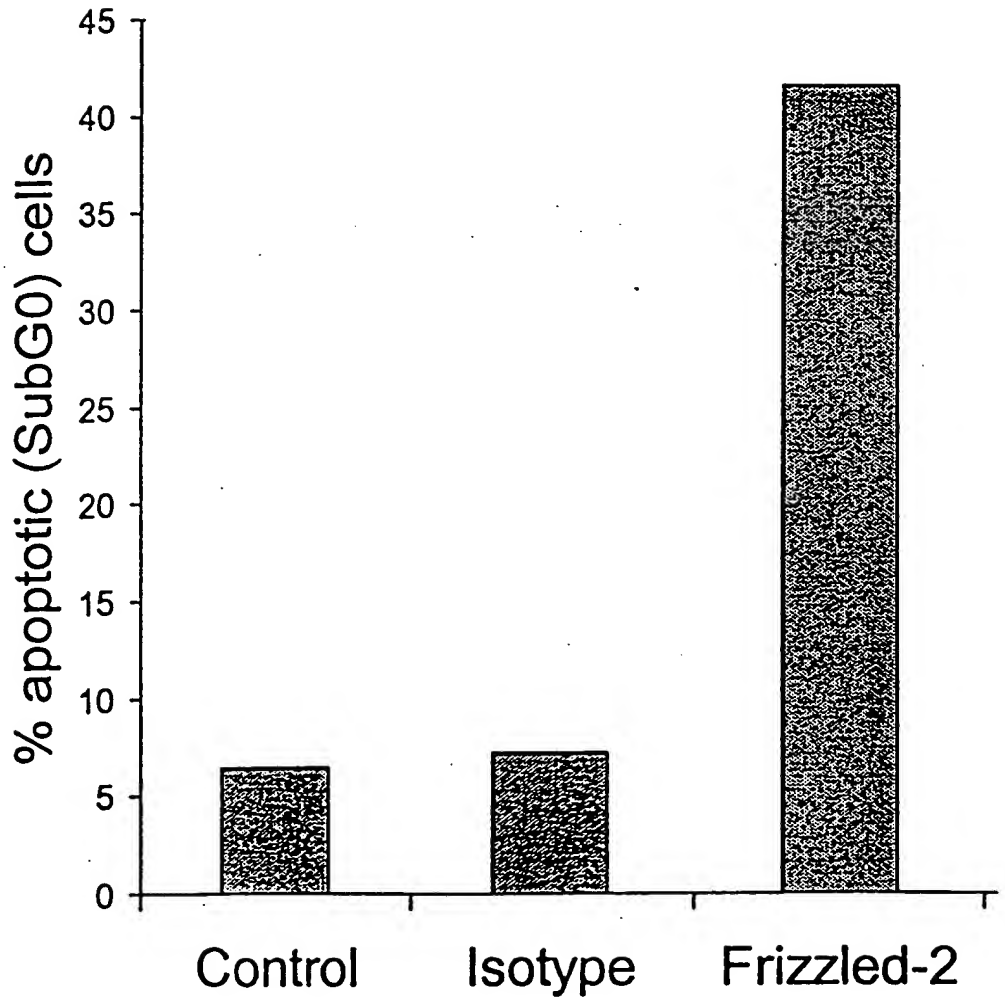
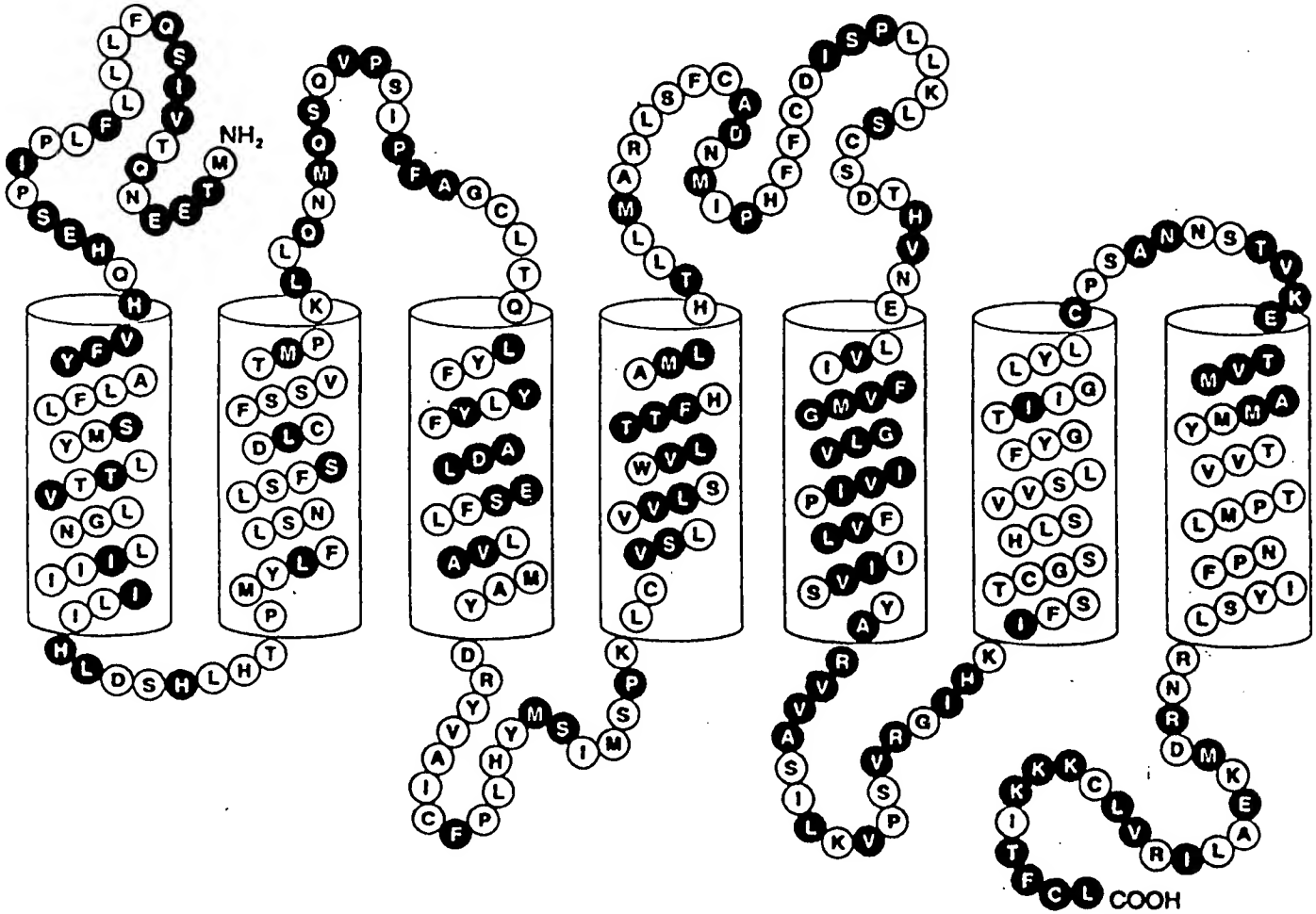


Figure 7



Graphical representation of an olfactory protein showing aminoterminal and three extracellular domain loops (from PCT WO 92/17585)

Figure 8a

|→ amino terminal domain

```
HFZ1     MAEEEAPKKSRAAGGGASWELCAGALSARLAEEGSGDAGGRRRPPVDPRRLARQLLLLLW
MFZ1     MAEEAAPSESRAAGR-LSLELCAEALPGRREEVGHEDTASHRRPRADPRRWASGLLLLLW
HFZ2     ----------------------------------------------MRPRSALPRLLLPLL
HFZ3     ----------------------------------------------MAMTWIVFSLWPLTV
MFZ3     ----------------------------------------------MAVSWIVFDLWLLTV
HFZ4     --------------------------------MAWRGAGPSVPGAPGGVGLSLGLLLQ
MFZ4     --------------------------------MAWPGTGPSSRGAPGGVGLRLGLLLQ
HFZ5     ------------------------------------------MARPDPSAPPSLL--LLL
HFZ6     ------------------------------------------------MEMFTFLLTCI
MFZ6     ------------------------------------------------MERSPFLLACI
HFZ7     ------------------------------------MRDPGAAAPLSSLGLCALVLA
MFZ7     ------------------------------------MRGPGTAASHSPLGLCALVLA
HFZ8     ----------------------------------------MEWGYLLEVTSLLAALAL
MFZ8     ----------------------------------------MEWGYLLEVTSLLAALAV
HFZ9     ----------------------------------------MAVAPL-RGALLLWQLLA
MFZ9     ----------------------------------------MAVPPLLRGALLLWQLLA
HFZ10    ----------------------------------------------MQRPGPRLWLVLQ

HFZ1     LLEAPLLLGVRAQAAGQGPGQGPGPGQQPPPPPQQQQSGQQYNGERGISVPDHGYCQPIS
MFZ1     LLEAPLLLGVRAQAAGQVSG----PGQQAPPPPQPQQSGQQYNGERGISIPDHGYCQPIS
HFZ2     LLPA--------------A-----------------GPAQFHGEKGISIPDHGFCQPIS
HFZ3     FMGHI-----------------------------------GGHSLFS--------CEPIT
MFZ3     FLGQI-----------------------------------GGHSLFS--------CEPIT
HFZ4     LLLLLG-------------------------------PARGFGDEEE------RRCDPIR
MFZ4     FLLLLR-------------------------------PTLGFGDEEE------RRCDPIR
HFZ5     LAQLVG-------------------------------RAAAASKAPV--------CQEIT
HFZ6     FLPLL--------------------------------RGHSLFT--------CEPIT
MFZ6     LLPLV--------------------------------RGHSLFT--------CEPIT
HFZ7     LLGAL----------------------------SAGAGAQPYHGEKGISVPDHGFCQPIS
MFZ7     LLGAL----------------------------PTDTRAQPYHGEKGISVPDHGFCQPIS
HFZ8     LQRSSG-------------------------------AAAASAKELA--------CQEIT
MFZ8     LQRSSG-------------------------------AAAASAKELA--------CQEIT
HFZ9     AGGAAL-------------------------------EIGRFDPERGR---GAAPCQAVE
MFZ9     TGGAAL-------------------------------EIGRFDPERGR---GPAPCQAME
HFZ10    VMGSCA-------------------------------AISSMDMERP----GDGKCQPIE
                                                                *:. :

HFZ1     IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCT-V
MFZ1     IPLCTDMAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCT-V
HFZ2     IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
HFZ3     LRMCQDLPYNTTFMPNLLNHYDQQTAALAMEPFHPMVNLDCSRDFRPFLCALYAPICM-E
MFZ3     LRMCQDLPYNTTFMPNLLNHYDQQTAALAMEPFHPMVNLDCSRDFRPFLCALYAPICM-E
HFZ4     ISMCQNLGYNVTKMPNLVGHELQTDAELQLTTFTPLIQYGCSSQLQFFLCSVYVPMCTEK
MFZ4     IAMCQNLGYNVTKMPNLVGHELQTDAELQLTTFTPLIQYGCSSQLQFFLCSVYVPMCTEK
HFZ5     VPMCRGIGYNLTHMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPDLRFFLCTMYTPICLPD
HFZ6     VPRCMKMAYNMTFFPNLMGHYDQSIAAVEMEHFLPLANLECSPNIETFLCKAFVPTCI-E
MFZ6     VPRCMKMTYNMTFFPNLMGHYDQGIAAVEMGHFLHLANLECSPNIEMFLCQAFIPTCT-E
HFZ7     IPLCTDIAYNQTILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
MFZ7     IPLCTDIAYNQTILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
HFZ8     VPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPDLKFFLCSMYTPICLED
MFZ8     VPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPDLKFFLCSMYTPICLED
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Figure 8b

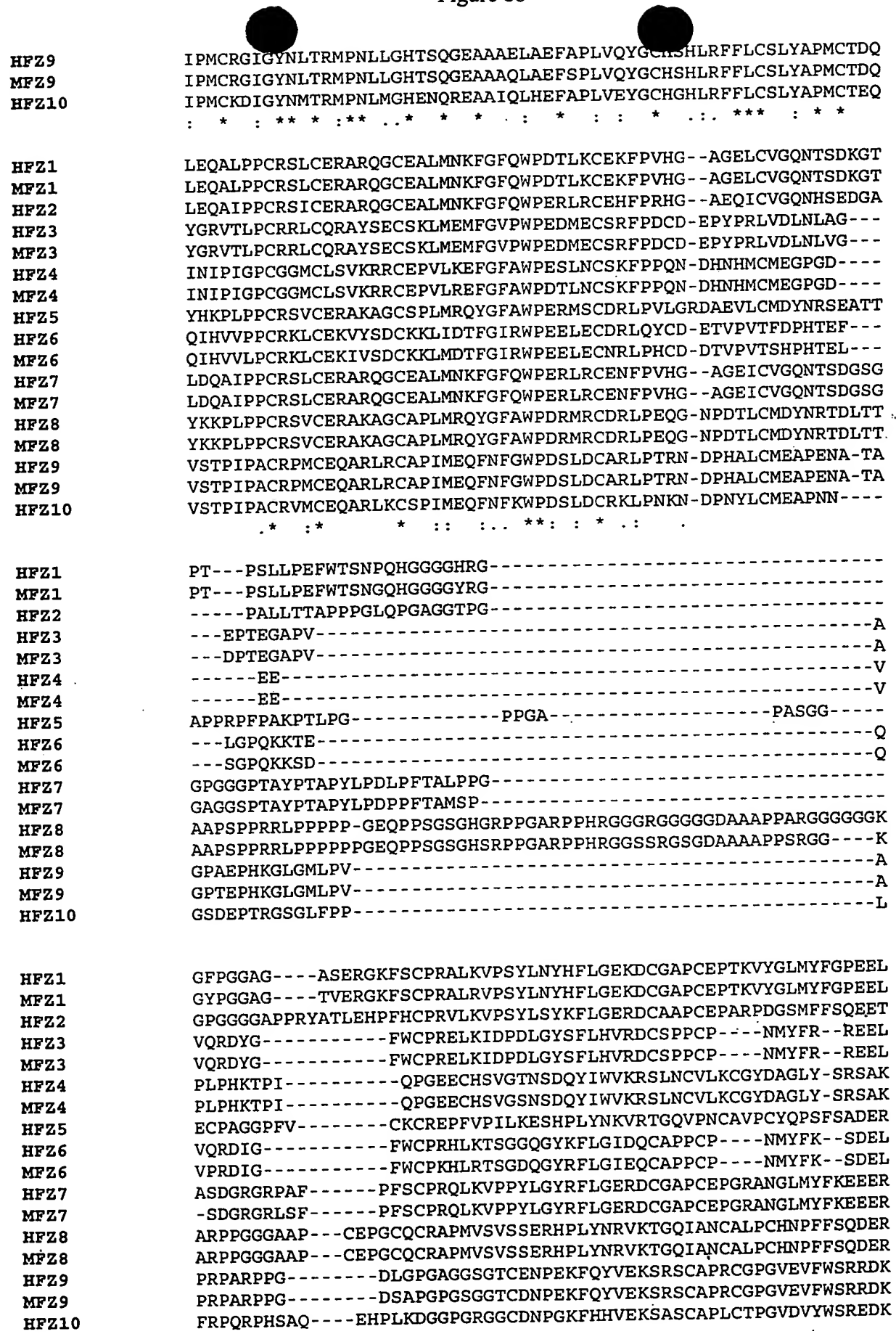
HFZ9 IPMCRGIGYNLTRMPNLLGHTSQGEAAAELAEFAPLVQYGCHSHLRFFLCSLYAPMCTDQ
MFZ9 IPMCRGIGYNLTRMPNLLGHTSQGEAAAQLAEFSPLVQYGCHSHLRFFLCSLYAPMCTDQ
HFZ10 IPMCKDIGYNMTRMPNLMGHENQREAAIQLHEFAPLVEYGCHGHLRFFLCSLYAPMCTEQ
HFZ1 LEQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHG--AGELCVGQNTSDKGT
MFZ1 LEQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHG--AGELCVGQNTSDKGT
HFZ2 LEQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFPRHG--AEQICVGQNHSEDGA
HFZ3 YGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDCD-EPYPRLVDLNLAG---
MFZ3 YGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDCD-EPYPRLVDLNLVG---
HFZ4 INIPIGPCGGMCLSVKRRCEPVLKEFGFAWPESLNCSKFPPQN-DHNHMCMEGPGD----
MFZ4 INIPIGPCGGMCLSVKRRCEPVLREFGFAWPDTLNCSKFPPQN-DHNHMCMEGPGD----
HFZ5 YHKPLPPCRSVCERAKAGCSPLMRQYGFAWPERMSCDRLPVLGRDAEVLCMDYNRSEATT
HFZ6 QIHVVPPCRKLCEKVYSDCKKLIDTFGIRWPEELECDRLQYCD-ETVPVTFDPHTEF---
MFZ6 QIHVVLPCRKLCEKIVSDCKKLMDTFGIRWPEELECNRLPHCD-DTVPVTSHPHTEL---
HFZ7 LDQAIPPCRSLCERARQGCEALMNKFGFQWPERLRCENFPVHG--AGEICVGQNTSDGSG
MFZ7 LDQAIPPCRSLCERARQGCEALMNKFGFQWPERLRCENFPVHG--AGEICVGQNTSDGSG
HFZ8 YKKPLPPCRSVCERAKAGCAPLMRQYGFAWPDRMRCDRLPEQG-NPDTLCMDYNRTDLTT
MFZ8 YKKPLPPCRSVCERAKAGCAPLMRQYGFAWPDRMRCDRLPEQG-NPDTLCMDYNRTDLTT
HFZ9 VSTPIPACRPMCEQARLRCAPIMEQFNFGWPDSLDCARLPTRN-DPHALCMEAPENA-TA
MFZ9 VSTPIPACRPMCEQARLRCAPIMEQFNFGWPDSLDCARLPTRN-DPHALCMEAPENA-TA
HFZ10 VSTPIPACRVMCEQARLKCSPIMEQFNFKWPDSLDCRKLPNKN-DPNYLCMEAPNN----
HFZ1 PT---PSLLPEFWTSNPQHGGGGHRG----------
MFZ1 PT---PSLLPEFWTSNGQHGGGGYRG----------
HFZ2 -----PALLTTAPPPGLQPGAGGTPG----------
HFZ3 ---EPTEGAPV----------A
MFZ3 ---DPTEGAPV----------A
HFZ4 ------EE----------V
MFZ4 ------EE----------V
HFZ5 APPRPFPAKPTLPG----------PPGA----------PASGG-----
HFZ6 ---LGPQKKTE----------Q
MFZ6 ---SGPQKKSD----------Q
HFZ7 GPGGGPTAYPTAPYLPDLPFTALPPG----------
MFZ7 GAGGSPTAYPTAPYLPDPPFTAMSP----------
HFZ8 AAPSPPRRLPPPPP-GEQPPSGSGHGRPPGARPPHRGGGRGGGGGDAAAPPARGGGGGGK
MFZ8 AAPSPPRRLPPPPPPGEQPPSGSGHSRPPGARPPHRGGSSRGSGDAAAAPPSRGG----K
HFZ9 GPAEPHKGLGMLPV----------A
MFZ9 GPTEPHKGLGMLPV----------A
HFZ10 GSDEPTRGSGLFPP----------L
HFZ1 GFPGGAG----ASERGKFSCPRALKVPSYLNYHFLGEKDCGAPCEPTKVYGLMYFGPEEL
MFZ1 GYPGGAG----TVERGKFSCPRALRVPSYLNYHFLGEKDCGAPCEPTKVYGLMYFGPEEL
HFZ2 GPGGGGAPPRYATLEHPFHCPRVLKVPSYLSYKFLGERDCAAPCEPARPDGSMFFSQEET
HFZ3 VQRDYG----------FWCPRELKIDPDLGYSFLHVRDCSPPCP----NMYFR--REEL
MFZ3 VQRDYG----------FWCPRELKIDPDLGYSFLHVRDCSPPCP----NMYFR--REEL
HFZ4 PLPHKTPI----------QPGEECHSVGTNSDQYIWVKRSLNCVLKCGYDAGLY-SRSAK
MFZ4 PLPHKTPI----------QPGEECHSVGSNSDQYIWVKRSLNCVLKCGYDAGLY-SRSAK
HFZ5 ECPAGGPFV--------CKCREPFVPILKESHPLYNKVRTGQVPNCAVPCYQPSFSADER
HFZ6 VQRDIG----------FWCPRHLKTSGGQGYKFLGIDQCAPPCP----NMYFK--SDEL
MFZ6 VPRDIG----------FWCPKHLRTSGDQGYRFLGIEQCAPPCP----NMYFK--SDEL
HFZ7 ASDGRGRPAF------PFSCPRQLKVPPYLGYRFLGERDCGAPCEPGRANGLMYFKEEER
MFZ7 -SDGRGRLSF------PFSCPRQLKVPPYLGYRFLGERDCGAPCEPGRANGLMYFKEEER
HFZ8 ARPPGGGAAP---CEPGCQCRAPMVSVSSERHPLYNRVKTGQIANCALPCHNPFFSQDER
MFZ8 ARPPGGGAAP---CEPGCQCRAPMVSVSSERHPLYNRVKTGQIANCALPCHNPFFSQDER
HFZ9 PRPARPPG--------DLGPGAGGSGTCENPEKFQYVEKSRSCAPRCGPGVEVFWSRRDK
MFZ9 PRPARPPG--------DSAPGPGSGGTCDNPEKFQYVEKSRSCAPRCGPGVEVFWSRRDK
HFZ10 FRPQRPHSAQ----EHPLKDGGPGRGGCDNPGKFHHVEKSASCAPLCTPGVDVYWSREDK

Figure 8c

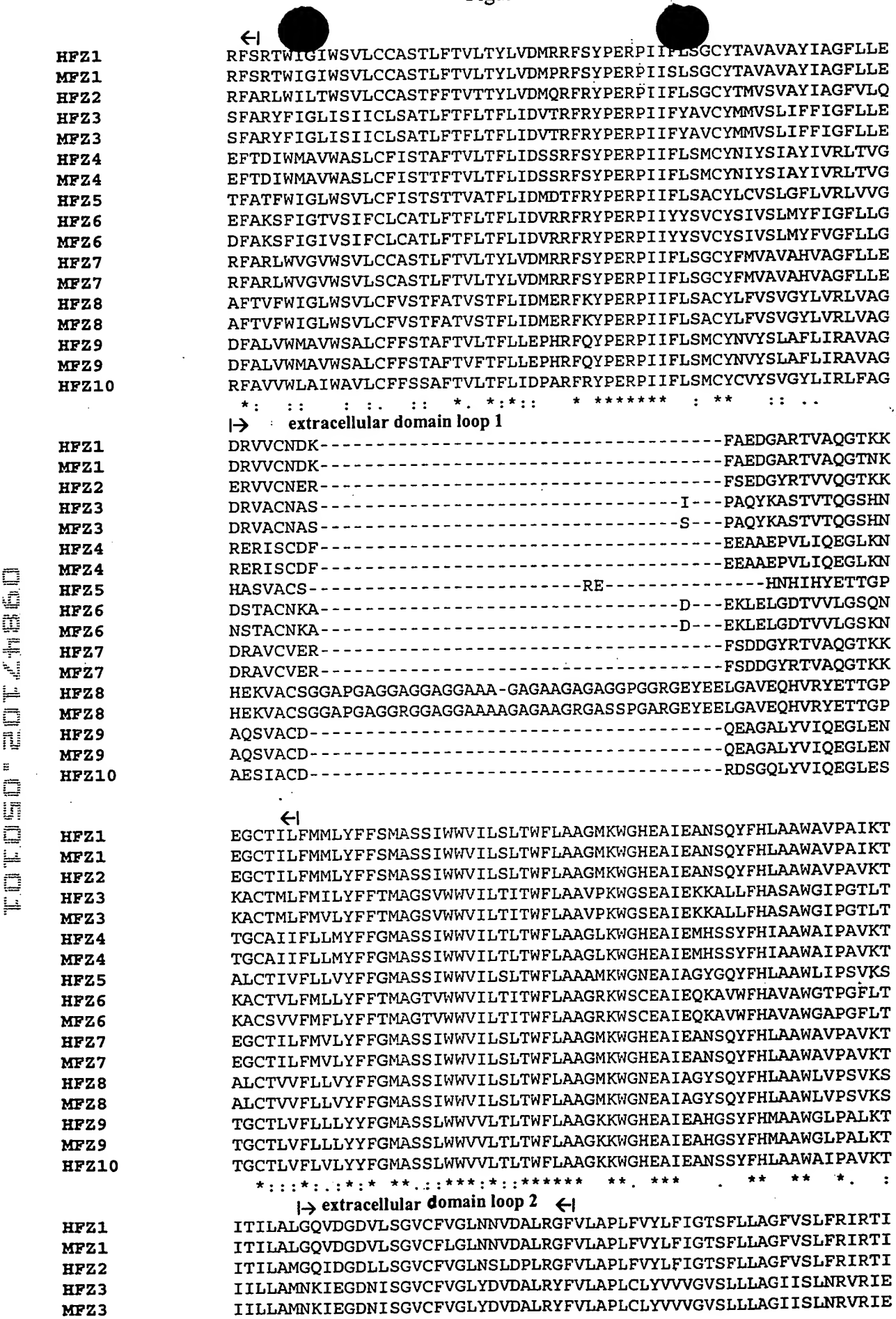
HFZ1 RFSRTWIGIWSVLCCASTLFTVLTYLVDMRRFSYPERPIIFLSGCYTAVAVAYIAGFLLE
MFZ1 RFSRTWIGIWSVLCCASTLFTVLTYLVDMPRFSYPERPIISLSGCYTAVAVAYIAGFLLE
HFZ2 RFARLWILTWSVLCCASTFFTVTTYLVDMQRFRYPERPIIFLSGCYTMVSVAYIAGFVLQ
HFZ3 SFARYFIGLISIICLSATLFTFLTFLIDVTRFRYPERPIIFYAVCYMMVSLIFFIGFLLE
MFZ3 SFARYFIGLISIICLSATLFTFLTFLIDVTRFRYPERPIIFYAVCYMMVSLIFFIGFLLE
HFZ4 EFTDIWMAVWASLCFISTAFTVLTFLIDSSRFSYPERPIIFLSMCYNIYSIAYIVRLTVG
MFZ4 EFTDIWMAVWASLCFISTTFTVLTFLIDSSRFSYPERPIIFLSMCYNIYSIAYIVRLTVG
HFZ5 TFATFWIGLWSVLCFISTSTTVATFLIDMDTFRYPERPIIFLSACYLCVSLGFLVRLVVG
HFZ6 EFAKSFIGTVSIFCLCATLFTFLTFLIDVRRFRYPERPIIYYSVCYSIVSLMYFIGFLLG
MFZ6 DFAKSFIGIVSIFCLCATLFTFLTFLIDVRRFRYPERPIIYYSVCYSIVSLMYFVGFLLG
HFZ7 RFARLWVGVWSVLCCASTLFTVLTYLVDMRRFSYPERPIIFLSGCYFMVAVAHVAGFLLE
MFZ7 RFARLWVGVWSVLSCASTLFTVLTYLVDMRRFSYPERPIIFLSGCYFMVAVAHVAGFLLE
HFZ8 AFTVFWIGLWSVLCFVSTFATVSTFLIDMERFKYPERPIIFLSACYLFVSVGYLVRLVAG
MFZ8 AFTVFWIGLWSVLCFVSTFATVSTFLIDMERFKYPERPIIFLSACYLFVSVGYLVRLVAG
HFZ9 DFALVWMAVWSALCFFSTAFTVLTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAG
MFZ9 DFALVWMAVWSALCFFSTAFTVFTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAG
HFZ10 RFAVVWLAIWAVLCFFSSAFTVLTFLIDPARFRYPERPIIFLSMCYCVYSVGYLIRLFAG
|→ extracellular domain loop 1
HFZ1 DRVVCNDK----------FAEDGARTVAQGTKK
MFZ1 DRVVCNDK----------FAEDGARTVAQGTNK
HFZ2 ERVVCNER----------FSEDGYRTVVQGTKK
HFZ3 DRVACNAS----------I---PAQYKASTVTQGSHN
MFZ3 DRVACNAS----------S---PAQYKASTVTQGSHN
HFZ4 RERISCDF----------EEAAEPVLIQEGLKN
MFZ4 RERISCDF----------EEAAEPVLIQEGLKN
HFZ5 HASVACS----------RE----------HNHIHYETTGP
HFZ6 DSTACNKA----------D---EKLELGDTVVLGSQN
MFZ6 NSTACNKA----------D---EKLELGDTVVLGSKN
HFZ7 DRAVCVER----------FSDDGYRTVAQGTKK
MFZ7 DRAVCVER----------FSDDGYRTVAQGTKK
HFZ8 HEKVACSGGAPGAGGAGGAGGAAA-GAGAAGAGAGGPGGRGEYEELGAVEQHVRYETTGP
MFZ8 HEKVACSGGAPGAGGRGGAGGAAAAGAGAAGRGASSPGARGEYEELGAVEQHVRYETTGP
HFZ9 AQSVACD----------QEAGALYVIQEGLEN
MFZ9 AQSVACD----------QEAGALYVIQEGLEN
HFZ10 AESIACD----------RDSGQLYVIQEGLES
HFZ1 EGCTILFMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKT
MFZ1 EGCTILFMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKT
HFZ2 EGCTILFMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT
HFZ3 KACTMLFMILYFFTMAGSVWWVILTITWFLAAVPKWGSEAIEKKALLFHASAWGIPGTLT
MFZ3 KACTMLFMVLYFFTMAGSVWWVILTITWFLAAVPKWGSEAIEKKALLFHASAWGIPGTLT
HFZ4 TGCAIIFLLMYFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKT
MFZ4 TGCAIIFLLMYFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKT
HFZ5 ALCTIVFLLVYFFGMASSIWWVILSLTWFLAAAMKWGNEAIAGYGQYFHLAAWLIPSVKS
HFZ6 KACTVLFMLLYFFTMAGTVWWVILTITWFLAAGRKWSCEAIEQKAVWFHAVAWGTPGFLT
MFZ6 KACSVVFMFLYFFTMAGTVWWVILTITWFLAAGRKWSCEAIEQKAVWFHAVAWGAPGFLT
HFZ7 EGCTILFMVLYFFGMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT
MFZ7 EGCTILFMVLYFFGMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT
HFZ8 ALCTVVFLLVYFFGMASSIWWVILSLTWFLAAGMKWGNEAIAGYSQYFHLAAWLVPSVKS
MFZ8 ALCTVVFLLVYFFGMASSIWWVILSLTWFLAAGMKWGNEAIAGYSQYFHLAAWLVPSVKS
HFZ9 TGCTLVFLLLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMAAWGLPALKT
MFZ9 TGCTLVFLLLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMAAWGLPALKT
HFZ10 TGCTLVFLVLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEANSSYFHLAAWAIPAVKT
|→ extracellular domain loop 2
HFZ1 ITILALGQVDGDVLSGVCFVGLNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
MFZ1 ITILALGQVDGDVLSGVCFLGLNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ2 ITILAMGQIDGDLLSGVCFVGLNSLDPLRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ3 IILLAMNKIEGDNISGVCFVGLYDVDALRYFVLAPLCLYVVVGVSLLLAGIISLNRVRIE
MFZ3 IILLAMNKIEGDNISGVCFVGLYDVDALRYFVLAPLCLYVVVGVSLLLAGIISLNRVRIE

Figure 8d

```
                tracellular domain loop 2 <-|
HFZ4     IVILIMRLVDADELTGLCYVGNQNLDALTGFVVAPLFTYLVIGTLFIAAGLVALFKIRSN
MFZ4     IVILIMRLVDADELTGLCYVGNQNLDALTGFVVAPLFTYLVIGTLFIAAGLVALFKIRSN
HFZ5     ITALALSSVDGDPVAGICYVGNQNLNSLRRFVLGPLVLYLLVGTLFLLAGFVSLFRIRSV
HFZ6     VMLLAMNKVEGDNISGVCFVGLYDLDASRYFVLLPLCLCVFVGLSLLLAGIISLNHVRQV
MFZ6     VMLLAMNKVEGDNISGVCFVGLYDLDASRYFVLLPLCLCVFVGLSLLLAGIISLNHVRQV
HFZ7     ITILAMGQVDGDLLSGVCYVGLSSVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
MFZ7     ITILAMGQVDGDLLSGVCYVGLSSVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ8     IAVLALSSVDGDPVAGICYVGNQSLDNLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSV
MFZ8     IAVLALSSVDGDPVAGICYVGNQSLDNLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSV
HFZ9     IVILTLRKVAGDELTGLCYVASTDAAALTGFVLVPLSGYLVLGSSFLLTGFVALFHIRKI
MFZ9     IVVLTLRKVAGDELTGLCYVASMDPAALTGFVLVPLSCYLVLGTSFLLTGFVALFHIRKI
HFZ10    ILILVMRRVAGDELTGVCYVGSMDVNALTGFVLIPLACYLVIGTSFILSGFVALFHIRRV
         :  *  :  :  .*  ::*:*::.   .        **:  **     :.:*   ::  :*:::*  ::*
                                                         |-> extracellular domain loop 3

HFZ1     MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSY
MFZ1     MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSY
HFZ2     MKH--DGTKTEKLERLMVRIGVFSVLYTVPATIVIACYFYEQAFREHWERSWVSQHCKSL
HFZ3     IPL--EKENQDKLVKFMIRIGVFSILYLVPLLVVIGCYFYEQAYRGIWETTWIQERCREY
MFZ3     IPL--EKENQDKLVKFMIRIGVFSILYLVPLLVVIGCYFYEQAYRGIWETTWIQERCREY
HFZ4     LQK--DGTKTDKLERLMVKIGVFSVLYTVPATCVIACYFYEISNWALFRYSADDSNMAV-
MFZ4     LQK--DGTKTDKLERLMVKIGVFSVLYTVPATCVIACYFYEISNWALFRYSADDSNMAV-
HFZ5     IKQ--GGTKTDKLEKLMIRIGIFTLLYTVPASIVVACYLYEQHYRESWEAALTCACPGHD
HFZ6     IQH--DGRNQEKLKKFMIRIGVFSGLYLVPLVTLLGCYVYEQVNRITWEITWVSDHCRQY
MFZ6     IQH--DGRNQEKLKKFMIRIGVFSGLYLVPLVTLLGCYVYELVNRITWEMTWFSDHCHQY
HFZ7     MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVLACYFYEQAFREHWERTWLLQTCKSY
MFZ7     MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVLACYFYEQAFREHWERTWLLQTCKSY
HFZ8     IKQQDGPTKTHKLEKLMIRLGLFTVLYTVPAAVVVACLFYEQHNRPRWEATHNCPCLRDL
MFZ8     IKQQGGPTKTHKLEKLMIRLGLFTVLYTVPAAVVVACLFYEQHNRPRWEATHNCPCLRDL
HFZ9     MKT--GGTNTEKLEKLMVKIGVFSILYTVPATCVIVCYVYERLNMDFWRLRATEQPCAAA
MFZ9     MKT--GGTNTEKLEKLMVKIGVFSILYTVPATCVIVCYVYERLNMDFWRLRATEQPCTAA
HFZ10    MKT--GGENTDKLEKLMVRIGLFSVLYTVPATCVIACYFXEHLNMDYWKILAAQHKCKM-
         :          :  .**  ::*:::*:*:  **  **     ::  *  .  *          :.

                      <-|
HFZ1     AIPCPHLQAGGGAPPHPPMSPDFTVFMIKYLMTLIVGITSGFWIWSGKTLNSWRKFYTRL
MFZ1     AIPCPHLQGGGGVPPHPPMSPDFTVFMIKYLMT---------------LNSWRKFYTRL
HFZ2     AIPCP-----AHYTPR--MSPDFTVYMIKYLMTLIVGITSGFWIWSGKTLHSWRKFYTRL
HFZ3     HIPCP-------YQVTQMSRPDLILFLMKYLMALIVGIPSVFWVGSKKTCFEWASFFHGR
MFZ3     HIPCP-------YQVTQMSRPDLILFLMKYLMALIVGIPSIFWVGSKKTCFEWASFFHGR
HFZ4     -----------------------EMLKIFMSLLVGITSGMWIWSAKTLHTWQ-KCSNR
MFZ4     -----------------------EMLKIFMSLLVGITSGMWIWSAKTLHTWQ-KCSNR
HFZ5     TGQPR----AK---------PEYWVLMLKYFMCLVVGITSGVWIWSGKTVESWRRFTSRC
HFZ6     HIPCP-------YQAKAKARPELALFMIKYLMTLIVGISAVFWVGSKKTCTEWAGFFKRN
MFZ6     RIPCP-------YQANPKARPELALFMIKYLMTLIVGISAVFWVGSKKTCTEWAGFFKRN
HFZ7     AVPCP----PGHFPPM---SPDFTVFMIKYLMTMIVGITTGFWIWSGKTLQSWRRFYHRL
MFZ7     AVPCP----PRHFSPM---SPDFTVFMIKYLMTMIVGITTGFWIWSGKTLQSWRRFYHRL
HFZ8     QPDQA----RR---------PDYAVFMLKYFMCLVVGITSGVWVWSGKTLESWRSLCTRC
MFZ8     QPDQA----RR---------PDYAVFMLKYFMCLVVGITSGVWVWSGKTLESWRALCTRC
HFZ9     AGPGG----RRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSSKTFQTWQSLCYRK
MFZ9     TVPGG----RRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSSKTFQTWQSLCYRK
HFZ10    NNQTK----TLDC-LMAASIPAVEIFMVKIFMLLVVGITSGMWIWTSKTLQSWQQVCSRR
                                   ::*  :*                          *

HFZ1     TN--SKQGETTV------------------------------------------------
MFZ1     TN--SKQGETTV------------------------------------------------
HFZ2     TN--SRHGETTV------------------------------------------------
HFZ3     RKKEIVNESRQVLQEP-------------DFAQSLLRDPNTPIIRKSRGTSTQGTSTHAS
MFZ3     RKKEIVNESRQVLQEP-------------DFAQSLLRDPNTPIIRKSRGTSTQGTSTHAS
HFZ4     LVNSGKVKREKRGNGW---------------------------VKPGKGSE---------
MFZ4     LVNSGKVKREKRGNGW---------------------------VKPGKGNE---------
HFZ5     CC-RPRRGHKSGGA-----------------------------MA--AG-D---------
HFZ6     RKRDPISESRRVLQESCEFFLKHNSKVKHKKKHYKPSSHKLKVISKSMGTSTGATANHGT
MFZ6     RKRDPISESRRVLQESCEFFLKHNSKVKHKKKHGAPGPHRLKVISKSMGTSTGATTNHGT
```

Figure 8e

```
HFZ7      SH--SSKGETAV------------------------------------------------
MFZ7      SH--SSKGETAV------------------------------------------------
HFZ8      CW-ASKGAAVGGGAGA---------------------------TAAGGGGGPGGGGGGGP
MFZ8      CW-ASKGAAVGAGAGG---------------------------SGPGGSGP-------GP
HFZ9      IA--AGRARAKACRAP---------------------------GSYGRGTHC--------
MFZ9      MA--AGRARAKACRTP---------------------------GGYGRGTHC--------
HFZ10     LKKKSRRKPASVITSG---------------------------GIYKKAQH---------

HFZ1      ------------------------------------------------------------
MFZ1      ------------------------------------------------------------
HFZ2      ------------------------------------------------------------
HFZ3      STQLAMVDDQRSKAGSIHSKVSSYHGSLHRSRDGRYTPCSYRG--MEERLPHGSMS-RLT
MFZ3      STQLAMVDDQRSKAGSVHSKVSSYHGSLHRSRDGRYTPCSYRG--MEERLPHGSMS-RLT
HFZ4      ------------------TVV---------------------------------------
MFZ4      ------------------TVV---------------------------------------
HFZ5      -------------YPEASAALTGRTGPPGPAATYHKQVSLSHV-----------------
HFZ6      SAVAITSHDYLGQETLTEIQTSPETSMREVKADGASTPRLREQDCGEPASPAASIS-RLS
MFZ6      SAMAIADHDYLGQETSTEVHTSPEASVKEGRADRANTPSAKDRDCGESAGPSSKLSGNRN
HFZ7      ------------------------------------------------------------
MFZ7      ------------------------------------------------------------
HFZ8      GGGGGPGGGGGGSLYSDVSTGLTWRSGTAS-SVSYPKQMPLSQV----------------
MFZ8      GGGGGHGGGGGGSLYSDVSTGLTWRSGTAS-SVSYPKQMPLSQV----------------
HFZ9      -----------H---YKAPTVVLHMTKTDPSLENPTHL----------------------
MFZ9      -----------H---YKAPTVVLHMTKTDPSLENPTHL----------------------
HFZ10     ------------------PQKT-HHGKYEIPAQSPTCV----------------------

HFZ1      ------------------------------------------------------------
MFZ1      ------------------------------------------------------------
HFZ2      ------------------------------------------------------------
HFZ3      DHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTSMNRVIEEDGTSA------------
MFZ3      DHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTSMNRVIEEDGTSA------------
HFZ4      ------------------------------------------------------------
MFZ4      ------------------------------------------------------------
HFZ5      ------------------------------------------------------------
HFZ6      GEQVDGKG--QAGSVSESARSEGRISPKSDITDTGLAQSNNLQVPSSSEPSSLKGSTSLL
MFZ6      GRESRAGGLKERSNGSEGAPSEGRVSPKSSVPETGLIDCSTSQAASSPEPTSLKGSTSLP
HFZ7      ------------------------------------------------------------
MFZ7      ------------------------------------------------------------
HFZ8      ------------------------------------------------------------
MFZ8      ------------------------------------------------------------
HFZ9      ------------------------------------------------------------
MFZ9      ------------------------------------------------------------
HFZ10     ------------------------------------------------------------

HFZ1      -------------------
MFZ1      -------------------
HFZ2      -------------------
HFZ3      -------------------
MFZ3      -------------------
HFZ4      -------------------
MFZ4      -------------------
HFZ5      -------------------
HFZ6      VHPVSGVRKEQGGGCHSDT
MFZ6      VHSASRARKEQGAGSHSDA
HFZ7      -------------------
MFZ7      -------------------
HFZ8      -------------------
MFZ8      -------------------
HFZ9      -------------------
```